

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 07 DEC 2006

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| Applicant's or agent's file reference 219-MUM-2004 | | FOR FURTHER ACTION | | See Form PCT/PEA/416 |
| International application No. PCT/IN2005/000056 | | International filing date (day/month/year) 22.02.2005 | | Priority date (day/month/year) 23.02.2004 |
| International Patent Classification (IPC) or national classification and IPC INV. C07D209/88 | | | | |
| Applicant CADILA HEALTHCARE LIMITED | | | | |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | | | | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p> | | | | |
| Date of submission of the demand 19.09.2005 | | Date of completion of this report 06.12.2006 | | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | | Authorized officer Lauro, Paola Telephone No. +49 89 2399- | | |



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IN2005/000056

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-16 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**INTERNATIONAL PRELIMINARY REPORT
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|------|
| Novelty (N) | Yes: Claims | 1-16 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-16 |
| Industrial applicability (IA) | Yes: Claims | 1-16 |
| | No: Claims | |

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V.

1 Reference is made to the following document:

- D1: CHEN W-M ET AL: "SYNTHESIS AND CRYSTAL STRUCTURE OF CARVEDILOL" JIEGOU HUAXUE - CHINESE JOURNAL OF STRUCTURAL CHEMISTRY, CHINESE ACADEMY OF SCIENCES,, CN, vol. 17, no. 5, September 1998 (1998-09), pages 325-328, XP008061814 ISSN: 0254-5861
- D2: WO 02/00216 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; HIL) 3 January 2002 (2002-01-03) cited in the application
- D3: US 2002/143045 A1 (HILDESHEIM JEAN ET AL) 3 October 2002 (2002-10-03) cited in the application

2. Novelty

None of the cited documents discloses a process for preparing carvedilol wherein all of the following conditions are satisfied:

- 1) the ratio of the reagents
- 2) the reaction temperature
- 3) the organic solvent
- 4) the formation of a salt by reaction with an organic acid and its purification
- 5) the reaction with a base to form the free Carvedilol which is then purified

Novelty is therefore acknowledged re D1 to D3.

3. Inventive step

The problem underlying the present application appears to reside in the provision of an improved process for preparing Carvedilol.

D1 to D3 disclose a process wherein crystalline Carvedilol is prepared from an epoxide of formula (II) with a slight excess of the amine of formula (III) in an organic solvent under the temperature conditions indicated in the present application. The

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(SEPARATE SHEET)**

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result after precipitation and purification is crystalline Carvedilol.

In the process of the present application additional steps are required, namely the formation of a salt, its purification and the reaction with a base to get free Carvedilol and subsequent purification.

Since D1 to D3 appear to lead to crystalline Carvedilol with a satisfactory degree of purity, in the absence of any comparative evidence that the present process, which requires additional steps, can be seen as advantageous over the prior art (e.g. higher purity without any loss in yields), an inventive step cannot yet be acknowledged.

Re Item VI.

4. The following document:

D4: WO 2004/094378 A (MATRIX LABORATORIES LTD; RAMANJANEYULU, GORANTLA, SEETA; KUMAR, INDUKU) 4 November 2004 (2004-11-04)

has been published after the priority date of the present application and it is not therefore taken into account for the purposes of the present opinion.